REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the comments below.

Claims 1-15 are pending in the subject application and are presented for examination on the merits.

I. Objection to the Drawings

Applicant submits herewith a corrected drawing. Accordingly, this formal ground of objection is respectfully traversed.

II. Rejection of Claims 1-14 Under 35 U.S.C § 112, First Paragraph (Written Description)

Claims 1-14 are rejected under 35 U.S.C § 112, first paragraph. The Examiner alleges that the specification does not provide sufficient written description for the breadth of the claims.

This rejection is respectfully traversed as follows.

The present invention is directed to transgenic plants that have been transformed with a nucleic acid encoding a chimeric isoprenoid synthase polypeptide. Applicants' studies have shown that chimeric isoprenoid synthases that catalyze reaction products not obtained with naturally occurring (wild type) isoprenoid synthases are obtained by ligating conserved functional domains of different isoprenoid synthases together.

Isoprenoid synthase genes are found in a variety of organisms including bacteria, fungi and plants. In general, isoprenoid synthase genes and proteins isolated from a variety of sources ranging from plants to humans demonstrate highly conserved and distinct domain regions. The individual members of the isoprenoid synthase families are multi-domain proteins that catalyze the synthesis of particular biologically active chemical compounds. For any particular family

member, different protein domains catalyze different steps in the overall synthesis reaction. Each family member catalyzes the synthesis of a different chemical compound because each contains a different collection or arrangement of protein functional domains.

Swapping regions approximating exons between different terpene synthases has led to the identification of functional domains responsible for terminal enzymatic steps. For example, work performed on 5-epi-aristolochene synthase (TEAS) from *Nicotiana tabacum* (tobacco) and *Hyoscyamus muticus vetispiradiene* synthase (HVS) from henbane revealed that exon 4 and exon 6, respectively, were responsible for reaction product specificity. Combining functional domains resulted in novel enzymes capable of synthesizing new reaction products (U.S. Pat. No. 5,824,774).

The genes for chrysanthemyl diphosphate (CPP) synthase and farnesyl diphosphate (FPP) synthase from sagebrush, *Artemisia tridentata spiciformis*, were also isolated and characterized. These isoprenoid genes were also shown to contain the five conserved regions found in prenyltransferases that catalyze chain elongation. Similarly, three full-length cDNAs encoding putative isoprenoid synthases, FDS-1, FDS-2, and FDS-5, with greater than 89% similarity were isolated from a Big Sagebrush *Artemisia tridentata* cDNA library and demonstrated to contain conserved domains.

In a recent publication concerning domain swapping of *Citrus limon* monoterpene synthases, it was noted that "The study of chimeras derived from homologous proteins having different specificities constitutes a powerful tool to identify functions of structural domains. (Arch. Biochem. And Biophys., 411 (2003) 196-203, at 197; copy enclosed). The authors accredited Dr. Chappell and his colleague for their earlier contributions to this field of research, acknowledging Dr. Chappell's work in 1996 on domain swapping between subdomains of

sesquiterpene synthases as providing novel enzymes capable of synthesizing the products of either one or both of the parent enzymes. The work reported in this article confirmed Dr. Chappell's inventive concept, that these enzymes contain conserved domains that can be reorganized to provide novel chimeric enzymes.

Yet another article published a few months after the filing date of the present application, reports the use of domain swapping in monoterpenes to identify the regions of regiospecificity of the enzymes (Schalk et al., PNAS, 97(22):11948-11953 (Oct. 2000; copy enclosed)). Again, the authors generated chimeric enzymes using knowledge of the conservation of domain sequences to generate the chimeras. This article, like those discussed above, demonstrates that the skilled practitioner at the time of the invention knew of and how to manipulate the conservation of conservation of domains in these enzymes.

Thus, it is evident from Applicants' studies and the published work of others that isoprenoid synthase genes contains several highly conserved domain regions, although not all five domains are necessarily present in any particular isoprenoid gene. It is also clear from the present specifiactiuon and work of others that the isoprenoid synthase genes share domains that can be utilized to form chimeric constructs that encode isoprenoid synthases having altered activities.

The Examiner states that the present specification does not provide sufficient written description to convey to one of ordinary skill in the art that applicant was in possession of the claimed invention at the time of filing. The Examiner asserts that applicant does not describe all chimeric isoprenoid synthases within the scope of the claims and asserts that the examples provided in the specification are not representative of the genus.

Applicant respectfully disagrees with the Examiner. It is neither the point of nor is it required that a specification provide written description of all compounds within the scope of the claims. As pointed out by the Examiner the specification provides several examples of chimeric isoprenoid synthases that were generated using publicly available and well known information concerning the sequences and alignment of various isoprenoid synthase genes. As discussed above, information concerning the presence and location of conserved domains in other isoprenoid synthase genes is also available. The present specification describes how to use the known sequences and how to generate chimeric isoprenoid synthases based on the relative position of the five known domains, while providing a sufficient number of examples of chimeric synthases. The present claims are broad, but no broader that the written description.

Furthermore, claims 3 and 12 are directed to plant cells and transgenic plants that are transformed with specific chimeric iosprenoid synthases that are clearly described and exemplified in the specification. Yet the Examiner states that these claims are not supported by sufficient written description to persuade one of skill in the art that the applicant was in possession of the claimed invention. Clearly, the claims are supported by the written description.

Accordingly, the rejection of claims 1-15 under 35 U.S.C § 112, first paragraph is respectfully traversed.

II. Rejection of Claims 1-15 Under 35 U.S.C § 112, First Paragraph (Enablement)

Claims 1-15 stand rejected under 35 U.S.C § 112, first paragraph. The Examiner states that the specification is enabling for plant cells and plants comprising chimeric variants of TEAS and HVS, and quiescent synthases, but does not reasonably provide enablement for any chimeric synthase within the scope of the claims. The Examiner asserts that because applicants do not

teach all nucleic acid molecule encoding functional or nonfunctional domains that can be used to generate the claimed chimeric proteins, it does not provide an enabling disclosure of the claimed invention. The Examiner also asserts that without appropriate guidance the skilled practitioner would not know which domains can be combined in a chimera to provide a functional protein, and to a recent publication concerning the structure of a Snapdragon monoterpene synthase, which was shown to lack one of the five conserved domains.

Applicants respectfully disagree with the Examiner's conclusions. As discussed above, there is sufficient information in the specification and published information known to those skilled in the art concerning the conserved domains of isoprenoid synthase genes to enable the skilled practitioner to practice the claimed invention. That there may be some isoprenoid synthases that lack a given domain does not prevent the skilled practitioner from utilizing knowledge of other domains to create chimeric polypeptides. The present application teaches how to isolate and use the conserved domains to generate chimeric polypeptides having new activities. It is not necessary that every chimera within the scope of the claims be functional; it is only necessary that one of ordinary skill in the art have a reasonable expectation of success. The present application clearly provides sufficient guidance and provides sufficient examples to enable the skilled practitioner to generate other chimeras based on the teachings of the specification and knowledge of conserved domains. Moreover, there is an abundance of published data concerning the conservation of domains in these and related enzymes, which the skilled practitioner can use and indeed has used over the years to generate chimeric enzymes.

Furthermore, there is **no evidence** that these conserved domains from different plants will not tolerate chimerization as suggested by the Examiner. In fact, the genes for chrysanthemyl diphosphate synthase, a farnesyl diphosphate synthase from sagebush have been successfully

used to prepare a series of chimeric proteins in which the conserved domains were rearranged. See Erickson, et al., J. Am. Chem. Soc., 2003, 125(23):6886-8 (copy enclosed). The genes from other related enzymes in different plants have also been swapped, as is demonstrated by the enclosed journal articles. Thus, this art is not unpredictable as asserted by the Examiner and undue experimentation would not be required to generate chimera based on the teachings of the specification and knowledge of the conservation of domains of these proteins.

Accordingly, the rejection of claims 1-25 under 35 U.S.C § 112, first paragraph is respectfully traversed.

It is respectfully submitted that the present application is in condition for allowance, an early notification thereof being earnestly solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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